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UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

EASTERN DIVISION

UNITED STATES OF AMERICA,

Plaintiff,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., *et al.*

Defendants.

No. 5:18-CV-01005-JGB-KKx

PLAINTIFF'S SUPPLEMENTAL REPLY REGARDING THE DEFINITION OF AN HCT/P, 21 C.F.R. § 1271.3(d)

Trial: May 4 – 13, 2021

Honorable Jesus G. Bernal
United States District Judge

Defendants' supplemental brief (ECF No. 178) confirms that their flawed interpretation of 21 C.F.R. Part 1271 fails to follow ordinary canons of statutory construction and disregards the text, history, and purpose of Part 1271.

I. HCT/P is a Broad Definition; the SSPE is a Narrow Exception

Defendants argue that their stem cell products are HCT/Ps that qualify for the SSPE, because Defendants view the "relevant" HCT/P as consisting of only those cells that they intend to implant. *See* Defs.' Supp. Br. at 5. The Government does not dispute that Defendants' three products[1] qualify as HCT/Ps under 1271.3(d), which broadly encompasses cellular and tissue products at all stages, from recovery to implantation.[2] But simply meeting the definition of an HCT/P is not dispositive here. The flaw in Defendants' argument is that Section 1271.3(d) is a definition, not an exception to regulation. The only exception at issue—the SSPE—imposes a significant limitation on what can be done to an HCT/P after it has been removed by comparing the HCT/P implanted to the HCT/P that was removed.[3] *See* 21 C.F.R. § 1271.15(b) ("[R]emoves HCT/P's from an individual and implants such HCT/P's . . . ."). Defendants cannot qualify for the SSPE simply by disregarding this fundamental limitation.

Moreover, regardless of which HCT/P is considered the HCT/P removed (*i.e.*, adipose tissue or various cells that later comprise SVF), Defendants have not met their burden of showing that they satisfy the SSPE. First, if adipose tissue is considered the "HCT/P's removed," it is clear that, following Defendants' extensive manufacturing process, the SVF Product (which consists only of certain cells) is in no respect the "such

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[1] Notably, Defendants did not explain how their arguments applied to their Expanded SVF or SVF/Vaccinia products, perhaps because they realize that these products, to an even greater extent, can never qualify for the SSPE. *See generally* Defs.' Supp. Br.; *see also* Pl.'s Supp. Br. (ECF No. 179) at 4.

[2] Defendants appear to recognize that the HCT/P definition is broad enough to encompass adipose tissue, *See* Defs.' Supp. Br. at 3:6-7 ("[T]he articles that constitute HCT/Ps under Section 1271.3(d) can include human cells or tissues among other things.").

[3] Exceptions from the law, especially exceptions to a public health law, should be narrowly construed. *See United States v. Kanasco, Ltd*, 123 F.3d 209, 211-12 (4th Cir. 1997), *citing Spokane & Inland Empire R.R. v. United States*, 241 U.S. 344, 350, 60 L. Ed. 1037, 36 S. Ct. 668 (1916).

HCT/P" (*i.e.*, adipose tissue) that was removed. Second, even if only the SVF cells are considered the HCT/P removed, they are significantly changed as a result of Defendants' processing, and thus "such HCT/P" is not returned. Pl.'s Supp. Br. at 3-4.

II. Defendants Selectively Ignore the Regulatory Text

Defendants recognize that canons of statutory construction require that no part of a regulatory provision should be "superfluous, void, or insignificant." *See* Defs.' Supp. Br. at 1 (citing *TRW Inc. v. Andrews*, 534 U.S. 19, 31 (2001)). But Defendants then disregard this canon by arbitrarily "simplif[ying] the meaning" of HCT/P by stripping out the phrase "articles containing or consisting of" and redefining an HCT/P solely as "human cells or tissues intended for implantation." *See* Defs.' Supp. Br. at 3-5.[4] If HCT/Ps were simply "human cells or tissues intended for implantation," the definition would so state. But it does not; it refers to any article "*containing or consisting* of human cells or tissues that are intended for implantation . . . ." 21 C.F.R. § 1271.3(d) (emphasis added). The definition includes articles like Defendants' SVF Product, which *consists of* various types of *cells* intended for implantation, and adipose tissue, which *contains various types of cells* intended for implantation.[5] Pl.'s Supp. Br. at 2; *see also United States v. US Stem Cell Clinic*, 998 F.3d 1302, 1308 (11th Cir. 2021) ("The adipose tissue contains the stromal-vascular fraction, which consists of cells intended for implantation into a patient. Therefore, both adipose tissue and stromal-vascular fraction are HCT/Ps.").

Defendants cannot disregard the plain language "containing" simply because it forecloses their strained argument that removed adipose tissue is not an HCT/P.

[4] Contrary to their assertions during closing argument (Trial Tr. at 10:11-17 (Aug. 20, 2021)), Defendants did not argue that the limiting phrase, "intended for implantation . . . into a human recipient" should be read to modify the word "articles" instead of "human cells or tissues." *See generally* Defs.' Supp. Br.; *cf.* Pl.'s Supp. Br. at 1, n.1.

[5] The Government's textual analysis of the SSPE and HCT/P definition, *see* Pl.'s Supp. Br. at 2-3, was not intended to suggest that the SSPE analysis can be reduced to a simple determination of whether the HCT/P removed falls into the same definitional category (*e.g.*, consists of cells, etc.) as the HCT/P implanted. Rather, the textual analysis demonstrates that the Government's plain reading of the regulations is reasonable and permissible. A comparison of the definitional categories is but one of many factors considered in an actual, fact-intensive analysis of whether the HCT/P implanted is "such HCT/P" removed.

Defendants' subsequent SSPE analysis relies upon this inaccurate and self-serving revision of the definition, *see* Defs.' Supp. Br. at 4-5, and does not withstand scrutiny.

III. The Government's Interpretation Does Not Disregard Cellular Products

In addition to misinterpreting the HCT/P definition, Defendants wrongly contend that the Government's plain-language reading forecloses cells and cellular products from qualifying for the SSPE, because, according to Defendants, cells are always removed from a larger system. First, Defendants' contention is contradicted by the trial testimony of expert witness Dr. Carolyn Yong, who confirmed that it *is* possible to remove cells from an individual without removing tissue or any other parts of the individual's body. *See* Trial Tr. Day 4 (PM – Yong) at 18:2-10 (noting that a human ovocyte [*sic* – oocyte] is one such example of a cell that can be removed).

Second, Part 1271 was expressly developed to apply to human tissues and cells, and the plain language of the HCT/P definition accounts for both. FDA does not dispute that cells are primarily isolated from larger systems, such as tissue, but that does not mean that cellular products can never qualify for the SSPE. Tellingly, Defendants cannot point to any position taken by FDA in the regulatory history or interpretive guidance wherein the SSPE prohibits removing and re-implanting articles consisting solely of cells, because FDA has never taken such a position. *See, e.g.*, Trial Ex. 86, FDA, Guidance for Industry: Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception (Nov. 2017). Rather, FDA has long recognized that autologous cells can be removed from an individual. *See id.* at 5 ("FDA's view is that *autologous cells* or tissues *that are removed from an individual* and implanted into the same individual without intervening processing steps beyond rinsing, cleansing, sizing, or shaping, raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery.") (emphases added). The regulations do not foreclose the possibility of new techniques for cell or tissue removal, as FDA intended Part 1271 to provide "appropriate oversight for the wide spectrum of cellular and tissue-based products that are now marketed or e*nvisioned for the future*."

See, e.g., Trial Ex. 378, FDA, Proposed Approach to Regulation of Cellular and Tissue-Based Products, FDA Dkt. No. 97N 0068 (Feb. 28, 1997) (emphasis added).

IV. Under *Kisor*, the Government's View Is Reasonable and Persuasive

When interpreting regulations, a Court looks to "traditional tools" of construction, including the "text, structure, history, and purpose of a regulation." *Kisor v. Wilkie*, 139 S. Ct. 2400, 2415 (2019). If those traditional tools leave "only one reasonable construction," then this Court must "give . . . effect" to that understanding of the regulation. *Id.* Here, the Government's construction is clearly reasonable because the text, structure, history, and purpose of FDA's regulations make clear that the definition of HCT/P includes both adipose tissue removed from a patient and the various products containing SVF cells that Defendants implant.

As the Government explained above and in its Supplemental Brief, *see* Pl.'s Supp. Br. at 1-3, the text, structure, and purpose of the Part 1271 regulations compel a reading of the HCT/P definition that applies with equal force to both adipose tissue and Defendants' adipose tissue-derived cellular products. The regulatory history also clearly supports the Government's view. FDA intentionally defined HCT/P broadly to encompass cellular and tissue-based products at all stages of production. In the preamble to Part 1271, FDA stated, "[t]he definition of 'human cells, tissues, or cellular or tissue-based product' is intended to cover HCT/P's at all stages of their manufacture, from recovery through distribution." 66 Fed. Reg. 5447, 5448 (Jan. 19, 2001). The HCT/P definition also was intended to include "such diverse articles as unprocessed tissue, highly processed cells, and tissues that are combined with certain drugs or devices." *Id.* at 5455. FDA unquestionably intended HCT/P to encompass the adipose tissue removed here.

By contrast, Defendants' unsupported interpretation excluding adipose tissue is inconsistent with the regulatory text and structure, and stands at odds with FDA's overarching purpose of creating a comprehensive, tiered, risk-based approach to HCT/P regulation under Part 1271. *See* Pls' Supp. Br. at 1-3. Defendants' reading cannot be reconciled with the regulatory history of the SSPE or Part 1271, nor with *Kisor's*

commands to interpret the provisions at issue in light thereof.

Because the regulatory text forecloses Defendants' attempt to evade the FDCA's requirements, this Court need not consider whether FDA's plain reading of its regulation is entitled to deference under *Kisor* and *Auer v. Robbins*, 519 U.S. 452 (1997). But even if this Court were to conclude that the regulations are ambiguous, it should defer to FDA's reasonable and permissible reading of the regulatory framework that it developed and administers. Federal courts have "often deferred to agencies' reasonable readings of genuinely ambiguous regulations." *Kisor*, 139 S. Ct. at 2408; *see Auer*, 519 U.S. at 461; *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410, 414 (1945). *Auer* deference is particularly warranted here, where the agency's interpretation "necessarily require[s] significant expertise and entail[s] the exercise of judgment grounded in policy concerns." *See Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994).

Although Defendants' process for creating cellular SVF drug products does not qualify for the regulatory exception they claim, that legal fact does not foreclose legitimate research in this area. Can stem cell therapies derived from a patient's own body be lawfully marketed for the treatment of various diseases or conditions? Yes—so long as those articles can be shown to be safe and effective under FDA's approval pathway for drugs and biological products. Can stem cell therapies derived from a patient's own body be lawfully and ethically studied in humans? Yes—so long as an Investigational New Drug Application is in effect to study and administer the investigational product to human subjects under FDA oversight. Can Defendants evade a regulatory framework designed to protect the public health by misreading the plain definition of an HCT/P and a narrow exception intended for surgeries? No.

Dated: September 1, 2021

Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 1st day of September, 2021, I electronically filed a true and correct copy of the foregoing PLAINTIFF'S SUPPLEMENTAL REPLY REGARDING THE DEFINITION OF HCT/P through the Court's CM/ECF system, which will send a notice of electronic filing to the following counsel of record listed below:

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